

1 -- 60. A method for determining a physiological characteristic of a biological  
2 material, comprising:  
3 irradiating a sample of a biological material with radiation to produce return  
4 radiation from the sample, wherein the return radiation is modulated by the sample;  
5 monitoring a first portion of the modulated return radiation at a first distance from  
6 the sample;  
7 monitoring a second portion of the modulated return radiation at a second distance  
8 from the sample;  
9 processing the first and second portions of the modulated return radiation, using a  
10 predictive model, to determine a physiological characteristic of the sample;  
11 wherein the predictive model is multivariate.--

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### REMARKS

Pursuant to the Office Action of December 7, 1998, an affirmative of the provisional election of Group I was requested, objections to the specification were made, and various claims were rejected under Sections 112, 102(b), 102(e) and 103(a). However, claims 8-10, 25-28, 35, 40, 42, 49 and 51 were found to be allowable if rewritten independent form including all of the limitations of the base claim and any intervening claims. All of these issues are addressed below, although in a slightly different order than that presented in the Office Action.

Preliminarily, Applicants confirm election of Group I. Thus, claims 43-47 of Group II have been withdrawn from further consideration. Moreover, as Applicants have added new claims 57-60, claims currently pending in the instant application are 1-42 and 48-60.

As for the objections to the specification, Applicants have amended the abstract to shorten its length, and the disclosure to provide brief descriptions of FIGS. 2(a), 2(b), 2(c), 3(a) and 3(b). Also, various inadvertent typographical errors in the specification have been corrected.

As for the conditionally allowed claims 8-10, 25-28, 35, 40, 42, 49 and 51, Applicants have rewritten these claims to include all the limitations of the base claim and any intervening claims to place them in condition for allowance.

Regarding the rejection under Section 112, Applicants appreciate the Examiner's comments and have rewritten claims 32, 33 and 56 to provide for proper antecedent bases. Claims 52 and 54 have also been amended to provide for proper antecedent basis.

I. Claims Defining Patentable Subject Matter Over Zuckerman Cited Under Section 102(b):

Regarding the rejection under Section 102(b), Applicants submit that claims 1, 2, 4-7, 11, 18, 30, 31, 33, 34, 39, 41, 48, 50 and 52 define patentable subject matter over Zuckerman (U.S. Pat. 5,495,850). Contrary to the Examiner's position (Office Action of 12/8/98, par. 6), there is no relevant disclosure in Zuckerman of monitoring return radiation from the sample analyzed, nor monitoring such return radiation from a first and a second distances, as claimed by Applicants.

To begin with, Zuckerman proposes a method to detect the oxygen concentration or partial pressure ( $PO_2$ ) in biological tissue and body fluids by measuring the fluorescence anisotropy of an  $O_2$ -quenchable probe substance (e.g., pyrenebuteric acid or pyrene) that is exogenous (i.e., foreign) to the body. In that regard, Zuckerman measures fluorescence emitted from the probe tip 68, namely, the fluorescence emitted by the  $O_2$  quenchable probe substance that is sealed between the glass fiber 66 (or the collimating lens 70) and an  $O_2$  permeable membrane 78 of the probe tip 68 (see, Col. 10, lines 16-24 and lines 30-33). There is no mention whatsoever by Zuckerman of using the UV light to illuminate the tissue in front of the catheter's tip. Thus, the fluorescence in Zuckerman is not from the analyzed sample, as alleged by the Examiner.

Moreover, while the Examiner relies on Col. 10, lines 1-48 of Zuckerman to conclude that the fluorescence is monitored at a first and a second distances from the fluorescing volume, it is also clear from Zuckerman that the emitted fluorescence is collected from the probe tip 68 by a single optical fiber (see, Col. 10, lines 45-48, "...fluorescence emission from the probe tip 68 returns along the single mode polarization-preserving glass fiber..."). Hence, Zuckerman

does not collect fluorescence at a first and a second locations, as alleged by the Examiner. With respect to the optical detectors 88A and 88B of Zuckerman, they detect linearly polarized vector components (parallel and perpendicular) of the returned fluorescence, which only resolves the emitted fluorescence into its linearly polarized components (parallel 86A and perpendicular 86B) to the plane of excitation. Thus, detectors 88A and 88B do not detect the fluorescence returned from a first and a second distances from the sample, as alleged by the Examiner.

In contrast, the inventions defined by independent method claims 1, 39, 41, 48 and 50 provide the steps of monitoring modulated return radiation from the sample at a first distance from the sample analyzed and at a second distance from the sample analyzed. Similarly, independent apparatus claim 52 provides for a second sensor, displaced by a second distance from the sample volume, adapted to monitor the return radiation from the sample analyzed and generate a second signal indicative of the intensity of the return radiation. Since Zuckerman disclosed neither the instant invention's monitoring of return radiation from the sample analyzed, nor the monitoring such return radiation at a first and a second distances from the sample analyzed, Zuckerman does not anticipate Applicants' invention as claimed. Accordingly, it is respectfully submitted that claims 1, 39, 41, 48 and 50 (as well as the claims depending therefrom) define novel subject matter over Zuckerman. Moreover, these claims define inventions that would not have been obvious in view of Zuckerman as it is devoid of any suggestion of monitoring the return radiation at a first and a second distances from the irradiated sample. Zuckerman neither disclosed this feature nor appreciated any advantage that could have been provided by such a feature.

## II. Claims Define Patentable Subject Matter over Alfano et al. Cited Under Section 102(e):

Without any admission on the alleged priority of Alfano et al. Under Section 102(e), Applicants hereinbelow distinguish the inventions of claims 1-7, 11-22, 30, 31, 36-38 and 53-56. In particular, independent method claims 1 and independent apparatus claims 53, 54, 55 and 56 include monitoring or measuring portions of the return radiation from a first and second distances from the irradiated sample. In this regard, Alfano et al., like Zuckerman distinguished above, lacks disclosure of this feature. In Col. 5, lines 53-63, Alfano et al.

describes the use of a trifurcated fiber optic bundle 47 having probe end 48, for both illumination and collection of fluorescence emitted from the illuminated slide. Although the fluorescence collected by the probe end 48 is split or divided into two portions that are transmitted to the second leg 51 and third leg 53 of the bundle 47 for purposes of filtering by two different filters 55 and 57, the fluorescence collected is nonetheless from the same, relatively small location on the slide, namely, the fluorescing area facing the probe end 48. In addition, Alfano et al. permits x-y movements of the slide S to permit scanning of a large area of the sample, such that each scan of a given location is processed separately and independently from preceding and subsequent scans performed on neighboring locations. Thus, Alfano et al. is devoid of a disclosure or teaching of irradiating a sample to produce return radiation and monitoring of that return radiation at a first distance and a second distance. Moreover, whereas Alfano et al. measures returned fluorescence on excised (dead) tissue (FIG. 2 and Col. 5), the invention of claim 31, is directed to living tissue.

Accordingly, it is respectfully submitted that claims 1, 53, 54, 55 and 56 (as well as the claims depending therefrom) define novel subject matter over Alfano et al. In addition, these claims define inventions that would not have been obvious in view of Alfano et al. as it is devoid of any suggestion of irradiating a sample to produce return radiation and monitoring that return radiation at a first and a second distances from the irradiated sample. Alfano et al. neither disclosed this feature nor appreciated any advantage that could have been provided by such a feature.

### III. Claims Patentable over Alfano et al. and over Zuckerman Cited Under Section 103(a):

Each of claims 23 and 24 depend from claim 12 which, in turn, depend from claim 1. Accordingly, the observations distinguishing Alfano et al. are hereby incorporated by reference in support of claims 23 and 24. In particular, because Alfano et al. failed to disclose or suggest monitoring return radiation at a first and a second distances from the sample analyzed.

Similarly, each of claims 29 and 32 has claim 1 as a base claim, and as such, define inventions that are novel and nonobvious over Zuckerman for the reasons set forth above,

which are hereby incorporated by reference. Like Alfano et al., Zuckerman failed to disclose or suggest monitoring return radiation at a first and a second distances from the sample analyzed.

It is therefore respectfully submitted that claims 23, 24, 29 and 32 also define patentable inventions over Alfano et al. and Zuckerman.

IV. New Claims 57-60:

New claims 57-60 have been added hereinabove. As new claim 57 depends from claim 1 and new claim 58 depends from claim 52, Applicants submit that claims 57 and 58 also define patentable subject matter.

New claim 59 substantially reflects claim 35, except that the physiological property of the tissue is ischemia, as opposed to hypoxia. Since claim 35 has been conditionally allowed, Applicants submit that new claim 59, incorporating the relevant limitations, is also in allowable form.

New claim 60 substantially reflects claim 49, except that the predictive model is a multivariate, as opposed to a multivariate linear regression. Since claim 49 has been conditionally allowed, Applicants submit that new claim 60, incorporating the relevant limitations, is also in allowable form.

V. Summary:

In view of the foregoing, Applicant requests reconsideration and allowance of claims 1-42 and 48-60. If any outstanding issues may be resolved over the telephone, the Examiner is requested to telephone the undersigned at (213) 622-7700, at extension 114.

Respectfully submitted,

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